

## Refractory Proctitis

Approximately 20-30% of patients with ulcerative colitis have disease confined to the rectum. There is a very small percentage of patients with Crohn's disease confined just to the rectum also.

About 40% of proctitis cases have a chronic relapsing course, and 6-7% have continuous disease activity. There is a significant group who fail to respond to 5-ASAs topically or orally, steroids topically or orally, immunomodulators or biologic therapy. Quality of life is generally poor considering the limited extent of inflammation, due to marked urgency, rectal pain, bleeding and sometimes incontinence. Proctocolectomy may then need to be considered and is a difficult option to accept for both clinician and patient because of the limited extent of inflammation.

In recent years, both topical thioguanine and topical tacrolimus have become options for treatment of refractory proctitis and there are publications for both.

## Rectal Thioguanine

Cases with refractory proctitis in the Netherlands, Queensland and New Zealand have been treated successfully with thioguanine administered by enema or suppository. A multicentre case series of 17 patients was reported in 2023 (1). All cases received a dose of 20mg. This was administered dissolved in 5ASA enemas in 7 patients of whom 5 had clinical response after a median of 7 days. Of 9 patients treated with thioguanine suppositories, 8 had a clinical response after a median of 14 days and the 9<sup>th</sup> patient had endoscopic mucosal healing. Treatment was stopped after a median of 32 days in responding patients.

In New Zealand, many more patients have now been treated with thioguanine 20mg dissolved in 50-100ml Pentasa enemas administered daily initially followed by dose tapering. Anecdotally, success rates are similar to those reported.

In view of the encouraging results reported for rectal thioguanine therapy, Douglas Pharmaceuticals are now developing thioguanine suppositories, to undergo clinical trials before commercial availability.

## Suggested practical use of rectal thioguanine

Open 1g/100ml Pentasa enema and discard approximately 50ml. Twist the top (nozzle) off the Pentasa enema, insert half of a 40mg tablet (to give a dose of 20mg) into the enema bottle and put the nozzle top back on. Wait for at least 10 minutes for the half tablet to dissolve. Shake the enema and then insert into the rectum. Administer on retiring to bed in the evening whilst lying down to help enema retention.

Repeat dosing daily until response or clinical remission, which usually takes about 1-2 weeks. Then the doses can be progressively less frequent aiming for the least frequent dosing to keep the proctitis in remission.

## Rectal Tacrolimus – Unfunded and more difficult to access in NZ than rectal thioguanine

The first report for tacrolimus was in 2008 and rectal tacrolimus ointment was prepared and given to 8 patients with resistant ulcerative proctitis (2). At 8 weeks, 6 of 8 had achieved remission. The second reported study of rectal tacrolimus paste was in 2017 in which a placebo-controlled trial showed that at 8 weeks, 8/11 patients achieved clinical response versus 1/10 in the placebo group (3).

The major difficulty with using tacrolimus ointment is that this needs to be prepared by a willing pharmacy, which is not always possible. Instructions are linked here. In 2020, a simple-to-prepare tacrolimus enema using powder from 1 mg capsules and tap water in a 60 ml syringe was reported in an open label study of 17 patients with refractory proctitis (12 UC, 5 Crohns) (4). Initial doses of 1-4mg tacrolimus daily were followed by thrice-weekly dosing for a median of 20 weeks. 94% tolerated treatment. 8/12 UC patients achieved endoscopic remission (and one further achieved endoscopic response). 3/5 CD patients achieved endoscopic response, including two with endoscopic remission.

In 2020, a 4-week multicentre randomised clinical trial was reported comparing tacrolimus 2mg and beclomethasone 3 mg suppositories in a total of 85 patients with refractory proctitis (4). Neither clinical remission (tacrolimus 46% vs beclomethasone 38%) nor endoscopic remission (tacrolimus 68% vs and beclomethasone 60%) were shown to be different, and adverse event rates were similar.

## References

1. Crouwel F, Simsek M, van Doorn AS, Mulder CJJ, Buiters HJC, Barclay ML, Florin TH, de Boer NK. Rectally Administrated Thioguanine for Distal Ulcerative Colitis: A Multicenter Case Series. *Inflamm Bowel Dis*. 2023 Jun 1;29(6):1000-1004. doi: 10.1093/ibd/izac195.
2. Lawrance IC, Copeland TS. Rectal tacrolimus in the treatment of resistant ulcerative proctitis. *Aliment Pharmacol Ther*. 2008 Nov 15;28(10):1214-20. doi: 10.1111/j.1365-2036.2008.03841.x. Epub 2008 Aug 30.
3. Lawrance IC, Baird A, Lightowler D, Radford-Smith G, Andrews JM, Connor S. Efficacy of Rectal Tacrolimus for Induction Therapy in Patients With Resistant Ulcerative Proctitis. *Clin Gastroenterol Hepatol*. 2017 Aug;15(8):1248-1255. doi: 10.1016/j.cgh.2017.02.027. Epub 2017 Mar 7.
4. Fehily SR, Martin FC, Kamm MA. Simple water-based tacrolimus enemas for refractory proctitis. *JGH Open*. 2019 Nov 14;4(4):561-564. doi: 10.1002/jgh3.12280.
5. Lie MRKL, Kreijne JE, Dijkstra G, Löwenberg M, van Assche G, West RL, van Noord D, van der Meulen-de Jong AE, Oldenburg B, Zaal RJ, Hansen BE, de Vries AC, Janneke van der Woude C; Dutch Initiative on Crohn and Colitis. No Superiority of Tacrolimus Suppositories vs Beclomethasone Suppositories in a Randomized Trial of Patients With Refractory Ulcerative Proctitis. *Clin Gastroenterol Hepatol*. 2020 Jul;18(8):1777-1784.e2. doi: 10.1016/j.cgh.2019.09.049. Epub 2019 Oct 11.

## Preparation Document Examples

PHARMACY DEPARTMENT ROYAL CHILDREN'S HOSPITAL MELBOURNE

### MISCELLANEOUS FORMULA (NON-STERILE)

#### INTRANET RECORD

<u>Name of preparation</u>	<u>Patient name and UR no (if applicable)</u>	<u>Strength</u>	<u>Source of Formula</u>
Tacrolimus ointment			

<u>Date of preparation</u>	<u>Quantity prepared</u>	<u>Prepared by</u>	<u>Batch No.</u>	<u>Expiry Date</u>
	200 g			3 mths

<u>Ingredients</u>	<u>Quantity</u>	<u>QD</u>	<u>Checked by</u>	<u>Manufacturer</u>	<u>Batch No.</u>
Tacrolimus 5mg caps	20				
Propylene glycol	2 mL				
White Soft paraffin to	200 g				

#### METHOD

Empty out capsules onto slab

Dissolve in 2 mL propylene glycol, incorporate into some of the white soft paraffin. Put this on a balance and weigh out white soft paraffin to make a final weight of 200g.

Incorporate thoroughly. Pack in brown glass jar.

#### LABEL CODE

TACR2

EXTRA LABELS: Caution – not to be take

MASTER CARD PREPARED:

(NSTacrolimus ointment doc/NSMaster/mg)

DATE: \_\_\_\_\_

Fremantle Hospital and Health Service			
Extemporaneous Product Master Sheet			
<b>NAME OF PRODUCT</b>	<b>STENGTH</b>	<b>FORMULARY</b>	<b>PACK SIZE</b>
Tacrolimus Rectal Ointment	0.03%	FHHS	200g
<b>LITERATURE REFERENCE</b>	<b>CONTAINER</b>	<b>STORAGE</b>	<b>EXPIRY</b>
Lawrence C, Copeland T. Rectal Tacrolimus in the treatment of resistant ulcerative proctitis. <i>Aliment Pharmacol Ther.</i> 28:1214 – 1220. Further reference available in Manufacturing.	Metal Tube	25C	28 days
<b>INDICATION</b>		<b>SAMPLE LABEL</b>	
Treatment of ulcerative proctitis			
<b>FORMULA</b>			
Tacrolimus Powder	60mg		
Propylene Glycol	5mL		
WSP 50%/LP 50% (Dermeze)	195g		
METHOD OF PREPERATION			
<u>Using aseptic technique in manufacturing</u>			
<ol style="list-style-type: none"> <li>1. Weigh 60mg tacrolimus powder (have weight checked by a pharmacist) 195g WSP50%/LP50% and measure 5mL propylene glycol.</li> <li>2. Transfer the tacrolimus powder to the glass slab and disperse with the propylene glycol.</li> <li>3. Triturate in the WSP50%/LP50% by method of doubling. Mix well.</li> <li>4. Using the ointment -tune -packer, package into 4X50g tubes. Put half the ointment in the ointment-tube- packer (i.e., make 2x50 gram tubes) then put the remaining half in to make another 2 x 5 gam tubes.</li> <li>5. Seal and label the tubes appropriately.</li> <li>6. Provide a calibrated applicator with each dispensing (3mL)</li> </ol>			
NOTES			
<ul style="list-style-type: none"> <li>• C&amp;A Caution Not To Be Taken – For Use In The Rectum Only Wear a mask and gloves while handling and preparing tacrolimus</li> <li>• Tacrolimus from complexes with cytoplasmic immunophilins, which block action of calcineurin in activated T cells. This prevents production of interleukin-2 and other cytokines, which normally stimulate T cell proliferation and differentiation.</li> <li>• Tacrolimus is a macrolide immunomodulator thus caution if patients have an allergy to other medications such as erythromycin, azithromycin, and clarithromycin.</li> </ul>			
Worksheet Compiled by:		<u>DATE</u>	
Worksheet Checked by:			